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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,589	01/15/2004	Keizo Koya	3211.1001-001	5403

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EXAMINER	
DELACROIX MUIRHEI, CYBILLE	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 11/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/758,589	KOYA ET AL.	
	Examiner	Art Unit	
	Cybille Delacroix-Muirheid	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-35 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-35 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 15 January 2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Claims 1-35 are presented for prosecution on the merits.

Information Disclosure Statement(s)

Applicant's Information disclosure statements received Jul. 1, 2004, July 16, 2004 and Oct. 18, 2004 have been considered. Please refer to applicant's copies of the 1449 submitted herewith.

Claim Rejection(s)-35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a limited number of multi-drug resistant cancers, does not reasonably provide enablement for all forms of cancers which are multi-drug resistant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could

not practice the invention without undue experimentation.

(1) The nature of the invention:

The claims are drawn to a method of treating a subject with a multi-drug resistant cancer by administering to the subject an effective amount of a compound of the claimed structural formulae.

(2) The state of the prior art

With respect to cancer, this a broad term which encompasses numerous forms of neoplastic diseases, each involving different types of tissues and organs and also includes blood-borne diseases. As recognized in the art, many different anti-neoplastic drugs are used to treat a variety of cancers, but there is no one drug, which is capable of treating all cancers in general, much less all forms of drug resistant cancers. Please see pages 1225-1229 of Goodman & Gilman's. Additionally, Calabresi et al. of Goodman & Gilman's teach that there are various mechanisms, which can lead to tumor cell resistance. Please see Goodman & Gilman's, page 1230.

(3) The relative skill of those in the art

The relative skill of those in the art is high. However, given the state of the art as set forth above, the artisan is currently unaware of any one particular anticancer agent that is effective against all cancer cell types or multi-drug resistant cell types.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical and cancer art is high. Additionally, the lack of significant guidance from the present specification or prior art with regard to the actual inhibition of all drug resistant cancer cell types in a mammal, including a human, with the

claimed compound as the active ingredient makes practicing the claimed method unpredictable.

(5) The breadth of the claims

The complex nature of the subject matter to which the present claims are directed is exacerbated by the breadth of the claim. The claims are broad and encompass treatment of a vast number of possible resistant cancer types including solid tumors as well as blood-borne tumors.

(6) The amount of direction or guidance presented

Applicant's specification is only enabled for inhibition of a limited number of cancer cell types such as myeloid leukemia, uterine sarcoma, melanoma and breast carcinoma. It does not enable one of ordinary skill in the art to use the claimed invention in the treatment of the numerous cancerous diseases covered by the limitation "multi-drug resistant cancer." Applicant's specification does not set forth a representative number of examples of drug resistant cancers, which would be inhibited by the claimed compound.

(7) The presence or absence of working examples

The working examples in the specification involve in vitro analysis of a compound of the invention. A compound of this invention has been shown to inhibit in vitro anti-cancer activity against 3 MDR cell lines, MES-SA/DX5, HL-60/TX1000, Bowes/OV2 and human leukemia cell lines. In vivo, a compound of the invention, in combination with another anti-tumor compound demonstrated activity against human breast carcinoma MDA-435 in Nude mice. Please see pages 79-94.

(8) The quantity of experimentation necessary

Since (1) the prior art recognizes that no one compound is capable of treating the vast number of possible cancers and that there are various distinct mechanisms which lead to tumor

cell resistance; (2) the specification shows anti-tumor activity against only a limited number of cell lines (i.e. four) and (3) since the claims are very broad and include treatment of any type of cancer cell in which resistance is achieved through various known, and even unknown, mechanisms, one of ordinary skill in the art would be burdened with undue experimentation to determine which resistant cancer cells would be inhibited by administration of the claimed compound to a mammal in need thereof.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 5-7, 13-17, 22-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites the limitation "a phenylene group" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 6 recites the limitation "wherein Y is...-C(R7R8), etc." in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim 7 recites the limitation "wherein Y is...-C(R7R8)-" in line 1, page 97. There is insufficient antecedent basis for this limitation in the claim.

Claim 13 recites the limitation "unsubstituted aliphatic group" in line 3, page 99. There is insufficient antecedent basis for this limitation in the claim.

Claim 14 recites the limitation "optionally substituted with at least one alkyl group" in line 5. There is insufficient antecedent basis for this limitation in the claim. Claim 1 requires substitution of an aliphatic group.

Claim 15 recites the limitation "unsubstituted alkyl group" in line 7. There is insufficient antecedent basis for this limitation in the claim.

Claim 17 recites the limitation ""Y' is bond" in lines 19-20, page 101. There is insufficient antecedent basis for this limitation in the claim.

Claim 22 recites the limitation "a phenylene group" in line 10. There is insufficient antecedent basis for this limitation in the claim.

Claim 23 recites the limitation "wherein Y is...--(CH2CH2)-...or a 1,4-phenylene group" in lines 11-12. There is insufficient antecedent basis for this limitation in the claim.

Claim 24 recites the limitation "wherein Y is...-C(R7R8)-" in line 2, page 105. There is insufficient antecedent basis for this limitation in the claim.

Claim 25 recites the limitations "unsubstituted aryl group" and "unsubstituted aliphatic group" in lines 10-11. There is insufficient antecedent basis for this limitation in the claim.

Claim 28 recites the limitation "R1 and R2 are each an unsubstituted phenyl group" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim 30 recites the limitation "R1 and R2 are both an..unsubstituted aliphatic group" in line 4, page 107. There is insufficient antecedent basis for this limitation in the claim.

Claim 31 recites the limitation "optionally substituted with at least one alkyl group" in line 6. There is insufficient antecedent basis for this limitation in the claim.

Claim 32 recites the limitation "unsubstituted alkyl group" in line 8. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejection(s)—35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

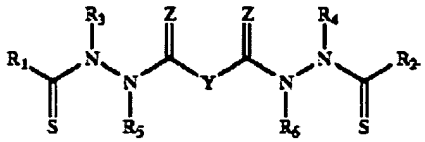
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

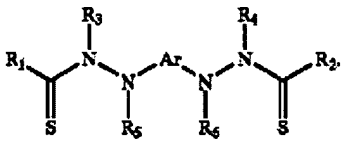
3. Claims 1-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koya et al., 6,762,204 and Koya et al., 6,800,660 and Koya et al., 6,924,312 in view of Calabresi et al., Goodman & Gilman's.

Koya et al. '204 and Koya et al. '660 and Koya et al. '312 disclose methods of treating cancer by administering to a patient in need thereof a composition comprising an effective amount of a compound of Formulae (I)-(VI):

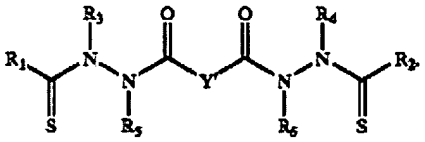
(I)



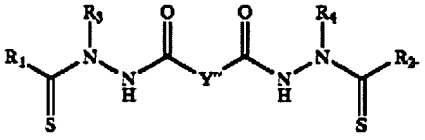
(II)



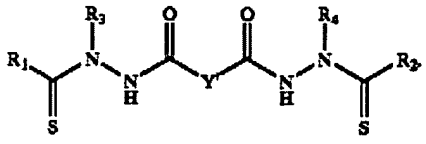
(III)



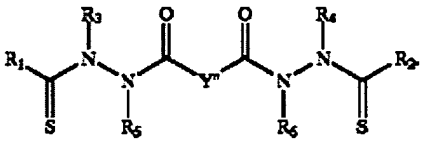
(IV)



(V)



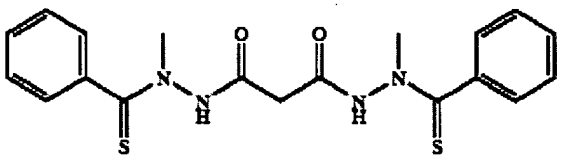
(VI)



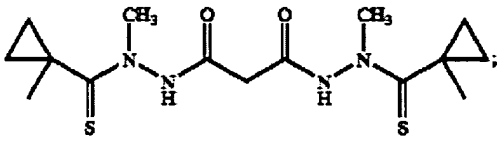
, wherein the substituents are defined therein.

Koya et al. disclose that the compounds may be administered alone (see '312, col. 2, line 64 to col. 3, line 20) as well as in combination with taxol or taxol analogs because the compounds increase the anti-cancer activity of the taxol or taxol analogs. See '204, col. 2; '660, col. 2; '312, col. 2). Preferred species of compounds include,

Compound (1)



and



. See '660, col. 1 and '312, col. 3.

However, Koya et al. '204 and '660 and '312 do not specifically disclose treating multi-drug resistant cancers. Yet, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Koya et al. to treat cancers which have become resistant because, in view of the desirable anti-cancer activity of the compounds (as suggested by Koya et al. '312), one of ordinary skill in the art would reasonably expect these compounds to be effective against tumor cells that have become resistant to treatment by other conventional chemotherapeutics. Furthermore, since the compounds, when administered with

taxol, increase the anti-cancer activity of taxol, one of ordinary skill in the art would reasonably expect a decrease in the likelihood that resistance to taxol would occur.

Concerning claim 18, where a chemotherapeutic agent other than taxol is optionally administered with the claimed compound. Calabresi et al. disclose various known chemotherapeutic agents (Table X-1). Additionally, Calabresi et al. teach at page 1230 that drugs are generally more effective when administered in combinations and may be synergistic through biochemical interactions. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the compounds of Koya et al. '204, '660 and '312 with other known chemotherapeutic agents taught by Calabresi et al. because one of ordinary skill in the art would reasonably expect such a combination to exert a more effective anti-tumor response. Such a modification would have been motivated by the reasonable expectation of achieving optimum tumor cell kill in drug resistant cancers.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-17, 30-34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,924,312. Although

the conflicting claims are not identical, they are not patentably distinct from each other because both the claims of the instant application and USPN '312 claim a method of treating cancer by administering to a subject in need thereof an effective amount of the claimed compounds.

The difference between the claims of the instant application and those of USPN '312 is that USPN '312 does not specifically claim treating multi-drug resistant cancer.

However, the scope of the claims of the instant application and of the claims of USPN '312 overlap because the claims of USPN '312 are broad and encompass all cancers including drug resistant cancers, therefore treatment of resistant cancers would be obvious in the methods of USPN '312. Finally, the claims suggest that the compounds have anti-cancer activity. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the compounds to subjects with drug-resistant cancer with the reasonable expectation that the compounds would demonstrate anti-cancer activity against the resistant cancer cells.

5. Claims 18-29, 35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 78-117 of U.S. Patent No. 6,800,660 and claims 85-125 of USPN 6,762,204 in view of Calabresi et al., supra.

The claims of both USPN '660 and '204 generally recite methods of treating cancer by administering to a subject in need thereof an effective amount of the claimed compounds in combination with taxol or a taxol derivative.

The claims do not recite a method of treating drug resistant cancers by administering the compounds with an anti-cancer agent other than taxol or its derivative. Yet, Calabresi et al. disclose various known chemotherapeutic agents (Table X-1). Additionally, Calabresi et al. teach

at page 1230 that drugs are generally more effective when administered in combinations and may be synergistic through biochemical interactions.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the compounds of Koya et al. '204, '660 with other known chemotherapeutic agents taught by Calabresi et al. because one of ordinary skill in the art would reasonably expect such a combination to exert a more effective anti-tumor response. Such a modification would have been motivated by the reasonable expectation of achieving optimum tumor cell kill in drug resistant cancers.

Conclusion

Claims 1-35 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Cybille Delacroix-Muirheid** whose telephone number is **571-272-0572**. The examiner can normally be reached on Mon-Thurs. from 8:30 to 6:00 as well as every other Friday from 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Christopher Low**, can be reached on **571-272-0951**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CDM
Oct. 30, 2005

Cybille Delacroix-Muirheid
Patent Examiner Group 1600